AR201-14202

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Health & Regulatory Affairs

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December 20, 2002

Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attention: Chemical Right-to-Know Program
Ethyl Cyanoacrylate (CAS 7085-85-0)
Registration Number

Dear Administrator Whitman:

On behalf of Henkel Loctite, I am pleased to submit the Test Plans and Robust Summary for ethyl cyanoacrylate under our commitment to the U.S. High Production Volume (HPV) Challenge Program.

If you require additional information, you may contact C. Judith Michaels at 860.571.5313.

Sincerely,

Mary Lynn Burke, CIH
Manager, Health & Regulatory Affairs
North America

enclosure

201-14202 A

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HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

TEST PLAN AND ROBUST SUMMARY

for

2-ETHYL CYANOACRYLATE

CAS No. 7085-85-0

Submitted by
Henkel Loctite
1001 Trout Brook Crossing
Rocky Hill, CT 06067

Prepared by C.J. Michaels

Henkel LOCTITE

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HPV VOLUNTARY PROGRAM

ETHYL CYANOACRYLATE

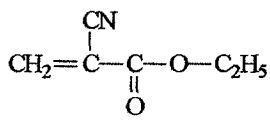
GENERAL INFORMATION

CAS Number
7085-85-0

Chemical Name
Ethyl cyanoacrylate

CAS Descriptor
Propenoic Acid, 2-cyano-, ethyl ester

Structural formula



Quantity
It is estimated that approximately 1,250,000 lbs. of ethyl cyanoacrylate is produced in the United States each year.

Use Pattern

Cyanoacrylates have been used worldwide for over 30 years. They are "instant" adhesives that bond to a variety of substrates including metals and plastics. They are applied as liquids and cure within seconds to minutes at room temperature by reacting in the presence of moisture or weakly alkaline materials forming inert, hard, polymeric solids with virtually no vapor pressure.

Approximately 80% of cyanoacrylate adhesives are the ethyl ester, and the majority of the remainder is the methyl ester. During the manufacture of cyanoacrylate esters, a small concentration of inhibitor is added to prevent polymerization. Additives such as thickeners and colorants and further inhibitors or activators may be added during the formulation of the adhesive to optimize their use for specific applications. A typical cyanoacrylate adhesive comprises 80-95% cyanoacrylate ester, 5-15% thickener, and 0.5-2% inhibitor.

Only a very small quantity is needed to create a bond, therefore the product is usually applied "drop by drop." This use characteristic together with its rapid polymerization to form an inert solid result in a very small potential for environmental damage.

Ethyl cyanoacrylate adhesives are widely used in the consumer and industrial markets.

Industrial applications include:

- The automotive and appliance industry where the major utility is attaching weather-stripping and trim strips, and for positioning rubber gaskets and other parts prior to assembly.
- The electronics industry for speaker magnet bonding, printed circuit boards, small component bonding.
- Manufacture of medical devices including catheters, and tubing.

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Cyanoacrylates are also widely used as consumer adhesives accounting for approximately 50% of the consumer adhesive market. The predominant applications are arts, crafts, and home repairs. They are also used for attaching and repairing artificial fingernails. Consumer cyanoacrylate adhesives are sold in very small packages, mostly 2 or 3-gram tubes or bottles. Thus, the opportunity for over-exposure and injury in the consumer market is small.

TEST PLAN

Ethyl Cyanoacrylate
CAS No. 7085-85-0

STUDY	INFORMATION (Y/N)	OECD Study	GLP	ACCEPTABLE (Y/N)	SIDS TESTING REQUIRED (Y/N)
Physical/Chemical Elements					
Melting Point	Yes	Unknown	Unknown	Yes	No
Boiling Point	Yes	Unknown	Unknown	Yes	No
Vapor Pressure	Yes	Unknown	Unknown	Yes	No
Partition Coefficient	Yes	Yes	Yes	Yes	No
Water Solubility	Yes	Yes	Yes	Yes	No
Environmental Fate and Pathways Elements					
Photodegradation	Yes	N/A	N/A	Yes	No
Stability in Water	Yes	Yes	Yes	Yes	No
Biodegradation	Yes	N/A	N/A	Yes	No
Fugacity	Yes	N/A	N/A	Yes	No
Ecotoxicity Elements					
Acute Fish	Yes	N/A	N/A	Yes	No
Toxicity to Aquatic Plants	Yes	N/A	N/A	Yes	No
Acute Toxicity to Aquatic Invertebrates	Yes	N/A	N/A	Yes	No
Health Elements					
Acute Toxicity	Yes	Equivalent	No	Yes	No
Genetic Tox. in vivo)	Yes	Unknown	Unknown	Yes	No
Genetic Tox. in vitro)	Yes	Unknown	Unknown	Yes	No
Repeat Dose Toxicity	Yes	N/A	N/A	Yes	No
Reproductive Toxicity	Yes	N/A	N/A	Yes	No
Developmental Tox.	Yes	N/A	N/A	Yes	No

JUSTIFICATION

Physical and Chemical Elements
The melting point, boiling point, and vapor pressure of ethyl cyanoacrylate are documented in standard adhesive textbooks. This data is considered adequate and no further testing is proposed. Testing to determine the partition coefficient failed to produce a value because of the reactive nature of the monomer.

Environmental Fate and Pathway Elements
Alkyl cyanoacrylates are among the most reactive monomers known in anionic polymerization. In the atmosphere and in biological systems, the available hydroxyl ions initiate rapid polymerization as evidenced by the rapid bonding to skin by instant adhesives comprising predominantly cyanoacrylate

esters. This property renders ethyl cyanoacrylate a useful adhesive and makes significant exposure to ethyl cyanoacrylate monomer improbable.

The risk of either environmental or biological exposure is further reduced by the manufacture, distribution, and use patterns. Ethyl cyanoacrylate is produced in closed systems and held at the manufacturing site in 55-gallon drums. After it is formulated for commerce, the predominant product size is less than one ounce. The product is used either drop-wise or as a small bead. Thus, an accidental discharge during distribution and use would be limited in size, and therefore neither environmental modeling nor testing is warranted.

Ecotoxicity Elements

For the reasons described in the previous section, the risk exposure of aquatic organisms is extremely limited. Furthermore testing in aquatic animals is not feasible. As detailed in the section on health effects, The National Toxicology Program (NTP) had difficulty in implementing a delivery system for dosing terrestrial animals and recommended that ethyl cyanoacrylate be removed from their priority testing list[1]. We therefore conclude no value would be derived from attempting to test ethyl cyanaocrylate in aquatic organisms.

Health Elements

Data is provided for acute oral and acute dermal toxicity, eye and skin irritation, and acute inhalation toxicity. No additional testing is planned. This is consistent with the position of the Environmental Defense Fund, which on its scorecard has recorded that there is adequate acute toxicity information for ethyl cyanoacrylate.

Reported[2] workplace exposure levels are up to 0.21 ppm for a 40-minute exposure, and an 8-hour time weighted average (TWA) of 0.06 ppm during the manufacture of ethyl cyanoacrylate. The maximum level reported when ethyl cyanoacrylate adhesive was used in a manufacturing process was 0.21ppm for an 8 hour TWA. Levels found in the Loctite manufacturing plant[3] ranged from 0.003 to 1.5 ppm for exposures of 15 minutes or less. Eight-hour time weighted averages were nearly always below 0.1 ppm. The American Conference of Governmental Industrial Hygienists (ACGIH) has established a TLV of 0.2 ppm (8-hour TWA) for ethyl cyanoacrylate. ACGIH has not suggested a short-term exposure limit or a ceiling value for ethyl cyanoacrylate.

Monomeric ethyl cyanoacrylate has an unpleasant acrid odor and is irritating to the eyes and mucous membranes of the nose, throat, and upper respiratory tract. The odor threshold is reported as 1 ppm and the irritation threshold 3-5 ppm[4]. These properties make even occasional exposures to toxic levels of ethyl cyanoacrylate improbable as discomfort propels one to leave any area where the airborne concentration of cyanoacrylate is appreciably above the irritation threshold.

The NTP has completed in-vivo and in-vitro genetic toxicity tests. No further testing in these categories is necessary.

As would be anticipated from this chemistry, dosing animals for repeated dose studies is problematic. Ethyl cyanoacrylate was listed by the Interagency Test Committee as a TSCA 4(e) priority chemical. After preliminary work, NTP[5] recommended its removal from the priority list citing "high reactivity of the chemical and the resulting difficulties in implementing the delivery of an effective concentration of the un-

[1] 60 FR 42987, 1995.
[2] Methyl cyanoacrylate and ethyl cyanoacrylate, Risk assessment document, UK Health and Safety Executive HMSO, Norwich UK, 2000.
[3] Paustenbach, D.,et al, Am. Ind. Hyg. Assoc J., 62, 70-79, 2001.
[4] McGee W.A., et al, Am. Ind. Hyg. Assoc J., 29, 558-561, 1968.
[5] 60 FR 42982-7, 1995

polymerized chemical to the test animals". NTP[1] also reported that they were unable generate a stable aerosol.

The United Kingdom Health and Safety Executive (HSE) has published a Risk Assessment Document on methyl and ethyl cyanoacrylate[2]. This risk assessment concluded that there are no grounds for concern of carcinogenicity at exposures below the threshold for chronic inflammatory responses in tissues at the site of contact. In addressing reproductive toxicity, HSE concluded "due to the reactive nature of ethyl cyanaocrylate, little systemic distribution is predicted following exposure by any physiological route. Furthermore, the overall pattern of toxicity data available suggests that the toxicological effects of ethyl cyanoacrylate would be largely restricted to local site of contact effects on the eyes and respiratory tract." Loctite concurs with these conclusions.

To address concerns that cyanoacrylates, including ethyl cyanoacrylate may act as respiratory sensitizers capable of inducing allergic asthma, Loctite Corporation sponsored two studies. The first was a survey to determine the airborne concentrations of cyanoacrylate in a manufacturing plant[3] and the second was an epidemiological[4] study that investigated the pulmonary effects of repeated occupational exposure to cyanoacrylates. The airborne concentrations determined in the first study provided the basis for the epidemiological study. The epidemiological study provided no evidence that those occupationally exposed to cyanoacrylate vapors during the manufacture and packaging of methyl and ethyl cyanoacrylate adhesives had any chronic pulmonary damage or that ethyl cyanoacrylate acted as a respiratory sensitizer. Subjects who had been exposed for a period of up to 18 years had no increased incidence of pulmonary obstruction compared to an unexposed population.

[1] NTP 1998 Annual report Table 6.
[2] Methyl Cyanoacrylate and Ethyl Cyanoacrylate, Risk Assessment Document, UK Health and Safety Executive HMSO, Norwich UK, 2000.
[3] Paustenbach, D.,et al, Am. Ind. Hyg. Assoc J., 62, 70-79, 2001.
[4] Goodman, M., et al, J. Toxic. & Environ. Hlth Part A, 59, 135-163, 2000.

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201-14102B

ROBUST SUMMARY

PHYSICAL/CHEMICAL ELEMENTS

1) MELTING POINT	-30°C
2) BOILING POINT	54-56°C
3) VAPOUR PRESSURE	<2torr @ 25°C

REFERENCES
Coover, H.W., Dreifus, D.W., and O'Connor, J.T., in Handbook of Adhesives, Irving Skeist editor, Van Nostrand Reinhold, 1990.

4) PARTITION COEFFICIENT

TEST SUBSTANCE:	Loctite Super Bonder 420. (Ethyl cyanoacrylate >99%)
Remarks	This is typical of monomeric ethyl cyanoacrylate as produced.
METHOD	OPPTS 830.7550
GLP (Y/N)	Yes
Year(study performed)	2002
Temperature	25°C
RESULTS	Log Pow Not determined. No ethyl cyanoacrylate could be detected in the water phase.
Remarks	Determination of the partition coefficient was attempted using EPA OPPTS method 830.7550. When the ethyl cyanaocrylate standard solution in n-octanol was being prepared, a white precipitate was observed. This was anticipated because of the long recognized sensitivity of cyanoacrylate esters towards trace quantities of nucleophiles including water, which promote rapid polymerization of the cyanoacrylate esters. The various n-octanol/cyanoacrylate mixtures were intimately contacted with water as required by the protocol for OPPTS 830.7550. Following centrifugation, the concentration of cyanoacrylate in each liquid phase was measured by reverse phase HPLC according to OSHA Method 55. No cyanoacrylate ester could be detected in any of the separated aqueous samples (Detection limit established as 2 µg/ml).
CONCLUSIONS	The partition coefficient for ethyl cyanaocrylate cannot be determined due to its ready polymerization in the presence of moisture.
DATA QUALITY	
Reliabilities	1
REFERENCES	Unpublished study, Datachem Laboratories, 2002

5) WATER SOLUBILITY

TEST SUBSTANCE:	Loctite Super Bonder 420 (Ethyl cyanoacrylate >99%)
Remarks	This is typical of monomeric ethyl cyanoacrylate as manufactured.
METHOD	OSHA Method 55
GLP (Y/N)	Yes
Year (Study performed)	2002
RESULTS	The study (OPPTS 830.7550) previously described to determine the octanol /water partition coefficient established that due to its tendency to polymerize rapidly on contact with moisture, the actual water solubility of ethyl cyanoacrylate is negligible (< 2µg/ml).
DATA QUALITY	
Reliabilities	1
REFERENCES	Unpublished study, Datachem Laboratories, 2002.

ENVIRONMENTAL FATE AND PATHWAY ELEMENTS

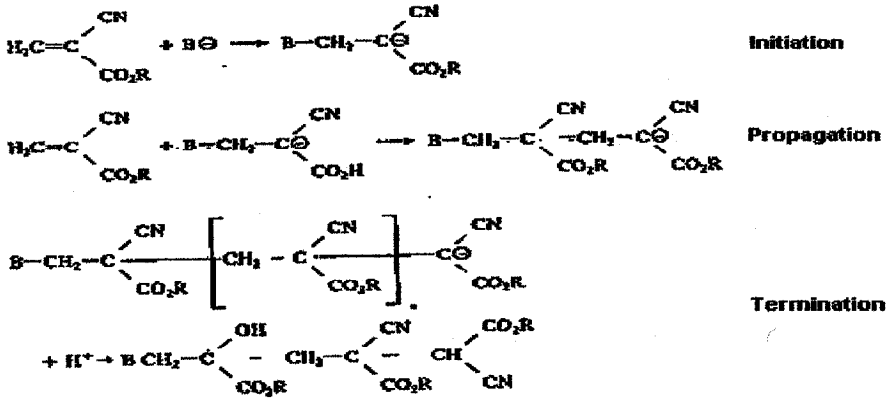
6) PHOTODEGRADATION

Theoretical modeling of the photodegradation of methyl 2-cyanoacrylate is reported in the National Toxicology Program's peer reviewed Hazardous Substance Database (HSDB). Based on the similarity in structure, its conclusions are applicable to ethyl 2-cyanoacrylate. It was estimated that vapor phase methyl 2-cyanoacrylate will be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals; the half-life for this reaction in air was estimated to be 5 days. It is unclear if this model takes into account the reactive nature of the molecule.

Cyanoacrylate esters are very reactive monomers that rapidly polymerize upon exposure to moisture. In the atmosphere and in biological systems, the available hydroxyl ions initiate rapid polymerization of ethyl cyanoacrylate monomer. The necessity to include polymerization inhibitors in the production distillation system further illustrates the reactive nature of the molecule.

The mechanism of polymerization is provided in Figure 1.

Figure 1
Mechanism of Ionic Polymerization of Cyanoacrylate Esters



The propagation rate constant for ethyl cyanoacrylate has been determined to be between $3x10^5$ and $6x10^5$ L∃mol^{-1}∃s^{-1} at 20°C in tetrahydofuran[1].

The probability of significant atmospheric releases is further reduced by its manufacture in a closed system and its use and distribution patterns. The largest size in which ethyl cyanoacrylate formulations are distributed in commerce in any significant amount is in one pound (454 g) bottles.

These circumstances make significant atmospheric levels of ethyl cyanoacrylate monomer improbable, and the development of any further data of no practical value.

[1] D.C. Pepper, B. Ryan, Makromol. Chem 395 1983. In Macromol. Rapid Commun. 17, 217-227, 1996

7) STABILITY IN WATER

The study (OPPTS 830.7550) to determine the water/n-octanol partition coefficient established that ethyl cyanoacrylate has negligible water solubility. This precludes any attempt to measure its stability in water.

8) TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY)

Because of the reactive nature of ethyl cyanoacrylate monomer and the manner in which it is distributed in commerce, fugacity information is of no practical value.

First, ethyl cyanoacrylate as a specialty chemical is not stored or transported in large containers, hence, significant release into the water supply is unlikely. Storage in the production facility is in 55 gallon drums (ethyl cyanaocrylate as produced), or 15 gallon plastic or metal containers (as formulated adhesives comprising approximately 90% ethyl cyanoacrylate). The most prevalent package size sold into the industrial market is a one-ounce bottle, followed by 20-gram bottle and then a one pound bottle. Small numbers of 2 kilogram bottles are distributed. Product for the consumer market is marketed in 2, 3, and 5 gram packages. Distribution in these small volume units greatly reduces the possibility of significant spills during transportation. Consistent with the package sizes, manufacturing operations utilizing ethyl cyanoacrylate adhesive apply it "by the drop" or as a small bead, thus, the opportunities for a large spill are limited.

Secondly, as previously demonstrated, ethyl cyanoacrylate monomer reacts upon contact with moisture. A stabilizer must be added to the receiving vessel during production to prevent immediate polymerization. Even after being stabilized for commercial purposes, if exposed to the atmosphere the monomer rapidly polymerizes to form an inert solid polymer. It is on this characteristic that the use of ethyl cyanoacrylate as a finger print developer is based. Polymerization occurs independent of the environmental compartment.

Finally, during the period in excess of 30 years that Loctite has been a leading manufacturer and marketer of ethyl cyanoacrylate and ethyl cyanoacrylate based products there has been, to our knowledge, no significant spill into the environment.

Based on the properties and marketing pattern discussed above and its long safe history in commerce, we maintain that development of information on fugacity is of theoretical value only, and is not justified.

9) BIODEGRADATION

Due to the previously described rapid polymerization, ethyl cyanoacrylate monomer does not exist in the environment in sufficient quantities for biodegradation to take place or for persistence to be an issue.

ECOTOXICITY ELEMENTS

10) ACUTE TOXICITY TO FISH
11) TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)
12) ACUTE TOXICITY TO AQUATIC INVERTEBRATES (E.G., DAPHNIA)

There is no practical opportunity for aquatic organisms to be exposed to significant volumes of ethyl cyanoacrylate.

First, ethyl cyanoacrylate as a specialty chemical is not stored or transported in large containers making significant release into the water supply unlikely. Storage in the production facility is in 55 gallon drums (ethyl cyanaocrylate as produced), or 15 gallon plastic or metal containers (as formulated adhesives comprising approximately 90% ethyl cyanoacrylate). The most prevalent package size sold into the industrial market is a one-ounce bottle, followed by a 20-gram bottle and then a one pound bottle. Small numbers of 2 kilogram bottles are distributed. Product for the consumer market is sold in 2, 3, and 5 gram packages. Distribution in these small volume units greatly reduces the possibility of significant spills during transportation. Consistent with the package sizes, manufacturing operations utilizing ethyl cyanoacrylate adhesive apply it "by the drop" or as a small bead, thus, the opportunities for a large spill are limited.

Secondly, as previously demonstrated, ethyl cyanoacrylate monomer reacts upon contact with moisture. A stabilizer must be incorporated in the receiving vessel during production to prevent immediate polymerization. Even after being stabilized for commercial purposes, if exposed to the atmosphere it rapidly polymerizes to form an inert solid polymer. It is on this characteristic that the use of ethyl cyanoacrylate as a finger print developer is based. Polymerization occurs independent of the environmental compartment

Based on the combination of these circumstances and that in the period in excess of 30 years that Loctite has been manufacturing ethyl cyanoacrylate products there has been, to our knowledge, no significant spill into the aquatic environment, we maintain that development of aquatic toxicity data is not warranted.

HEALTH ELEMENTS

13) ACUTE TOXICITY

A. Oral

TEST SUBSTANCE	Depend, IS 04E, Product 495, (Ethyl cyanoacrylate >95%, polymethyl methacrylate <5%).
Remarks	Test material was a commercial adhesive formulation representative of the formulations marketed at that time.
METHOD	
Type	Oral LD50 Limit test.
GLP (Y/N)	No (GLP introduced in 1978)
Year (study performed)	1973
Species/Strain	Albino Rats
Sex	Male
No.of animals per sex per dose	6
Vehicle	None
Route of administration	Oral intubation
Test Conditions.	The initial body weight ranged from 206-246 grams. The animals were fasted 18 hours prior to dosing. A single dose of 5000mg/kg was administered. Animals were observed during the day of dosing and daily thereafter for 14 days.
RESULTS	
Value	Oral LD50 >5000mg/kg
Number of deaths	1/6
Time of death	Day 4
Signs of intoxication	Death
Gross autopsy findings	Hemorrhagic lungs. Solid mass in stomach not adhered to stomach wall but too large to pass through pyloric valve. Cardiac portion of stomach distended. Food in intestine as in normal rat. One rat had dilated intestinal blood vessels.
DATA QUALITY	
Reliabilities	2
Remarks	Study not conducted under GLP but essentially the same as OECD 401

REFERENCES

Acute Oral Toxicity in Rats with Depend, IS 04E, (Product 495), Affiliated Medical Research, Inc. Princeton New Jersey, November 15, 1973.

B. Dermal Toxicity

TEST SUBSTANCE	04E, Depend, Product 495, (Ethyl cyanoacrylate >95%, polymethyl methacrylate <5%).
Remarks	Test material was a commercial adhesive formulation representative of the formulations marketed at that time.
METHOD	
Type	Dermal LD50 Limit test.
GLP (Y/N)	No (GLP introduced in 1978)
Year (study performed)	1973
Species/Strain	Albino Rabbits New Zealand Strain
Sex	Male
No.of animals per sex per dose	4
Vehicle	None
Route of administration	Dermal
Test Conditions.	The initial body weight ranged from 2034-2481grams. The animals were clipped free of dorsal hair. A single dose of 2000mg/kg was applied under rubber dental damming held in place with adhesive tape for 24 hours. Animals were observed during the day of dosing and daily thereafter for 14 days. At which time the y were sacrificed and examined for gross pathology.
RESULTS	
Value	Dermal LD50 >2000mg/kg
Number of deaths	0/4
Signs of Intoxication	None
Gross autopsy findings	Bandages and wrapping were initially bonded to skin, however after 14 days bandages were easily peeled off exposing a large open sore at site of application.
DATA QUALITY	
Reliabilities	2
Remarks	Study not conducted under GLP but essentially the same as OECD 402

REFERENCES

Acute Dermal LD50 Test in Rabbits with Depend, IS 04E, (Product 495), Affiliated Medical Research, Inc. Princeton New Jersey, December 5, 1973.

C. Dermal Irritation

TEST SUBSTANCE	Depend, Product 495, (Ethyl cyanoacrylate >95%, polymethyl methacrylate <5%).
Remarks	Test material was a commercial adhesive formulation representative of the formulations marketed at that time.
METHOD	
Type	Primary Dermal Irritation.
GLP (Y/N)	No (GLP introduced in 1978)
Year (study performed)	1973
Species/Strain	Albino Rabbits New Zealand Strain
Sex	Male
No.of animals	6
Vehicle	None
Test Conditions.	Skin on the dorsal surface was shaved free of hair by means of electric clippers. Twelve dorsal test areas were utilized; six were abraded down to, but not through, the dermis, using a hypodermic needle. The remaining test areas were left intact. 1"x1" gauze pads were saturated with 0.5g test liquid and applied to the dermal test areas. The gauze pads were left in place for 24 hours. The test areas were scored for dermal irritation immediately following the 24-hour exposure period and at 72 hours-post exposure, according to the method Draize[1].
RESULTS	The primary Irritation Index was determined to be 0.87. The test material is considered a mild irritant.
DATA QUALITY	
Reliabilities	2
Remarks	Study not conducted under GLP but essentially the same as OECD 404

REFERENCES

Primary dermal Irritation of Depend Adhesive in Rabbits (Product 495), Affiliated Medical Research, Inc. Princeton New Jersey, November 7, 1973.

[1] Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics, Assoc. of Food and Drug Officials of the U.S., Austin Texas, 1959.

D. Eye Irritation

TEST SUBSTANCE	Depend, Product 495, (Ethyl cyanoacrylate >95%, polymethyl methacrylate <5%).
Remarks	Test material was a commercial adhesive formulation representative of the formulations marketed at that time.
METHOD	
Type	Primary Eye Irritation.
GLP (Y/N)	No (GLP introduced in 1978)
Year (study performed)	1973
Species/Strain	Albino Rabbits, New Zealand Strain
Sex	Male
No.of animals	6
Vehicle	None
Test Conditions.	Approximately 0.1ml of the test liquid was introduced into the conjunctival sac of the right eye of each rabbit, the left eye served as an untreated control. The treated eyes were scored against the untreated eye according to the method of Draize[1] at 24, 48, and 72 hours after instillation of test liquid.
RESULTS	The group mean irritation score at 24 hours was 29.33, at 48 hours was 15.33 and at 72 hours was 9.66. According to the Draize evaluation, the test material was considered an irritant to the eye.
DATA QUALITY	
Reliabilities	2
Remarks	Study not conducted under GLP but essentially the same as OECD 405

REFERENCES

Primary Eye Irritation of Depend Adhesive (Product 495), Affiliated Medical Research, Inc. Princeton New Jersey, November 6, 1973.

[1] Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics, Assoc. of Food and Drug Officials of the U.S., Austin Texas, 1959.

E. Acute Inhalation

TEST SUBSTANCE	Superbonder 420, (Ethyl cyanoacrylate >99%)
Remarks	Test material is typical of monomeric ethyl cyanoacrylate as manufactured.
METHOD	
Type	Acute Inhalation
GLP (Y/N)	No (GLP introduced in 1978)
Year (study performed)	1982
Species/Strain	Wistar derived Albino Rats
Sex/No.of animals	5 male, 5 female
Test Conditions	Animals weighing 200-300g were exposed to 1.9g of test material during a 1-hour exposure period. During the first 30 minutes the test material was nebulized into the inhalation chamber after being warmed in a vessel submerged in water at 35-37°C. The temperature of the water bath was decreased to 25°C for the remaining 30 minutes. The concentration was estimated to be 21.11 mg/L/hour determined gravimetrically. Animals were observed for 14 days after exposure.
RESULTS	
Value	Inhalation LC50 <21.11mg/L (4123 ppm)/hour, nominal.
Number of deaths	7/10
Time of death	Days 1,2,2,4,4,3,2
Signs of intoxication	Animals were extremely irritable and showed signs of severe respiratory stress, eye irritation, and skin irritation. Several animals suffered nasal and ocular bleeding during the exposure period.
Autopsy findings	7 animals showed pulmonary, spleenic and intestinal hemorrhage. The remaining animal showed pulmonary and intestinal hemorrhage.
Remarks	The dosing level was determined gravimetrically, and it is unclear the extent to which polymerization was taken into account.
DATA QUALITY	
Reliabilities	2
Remarks	Study not conducted under GLP but essentially the same as OECD 403

REFERENCES

Acute inhalation study Superbonder 420, Ethyl Cyanoacrylate. Product Safety Labs, New Brunswick, NJ. December 14, 1982.

14) GENETIC TOXICITY IN VIVO (CHROMOSOMAL ABERRATIONS)

In 1993 and 1994 The National Toxicology (NTP) program performed four in-vivo cytogenic (micronucleus induction) testing in bone marrow cells. Two studies were performed in male Fischer 344 rats and two in male B6C3F1 mice. Animals were dosed intraperitoneally daily for 3 days at four dose levels ranging from 625 mg/kg to 2500 mg/kg. Cyclophosphamide, (25 mg/kg) was used as a positive control. Samples were taken at 96 hours post dosing in the rat studies and at either 72 or 96 hours in mice studies[1].

These studies have not been published but it was reported in the Federal Register[2] that "ethyl cyanoacrylate was not mutagenic in rodent bone marrow micronucleus tests."

15) GENETIC TOXICITY *IN VITRO* (GENE MUTATIONS)

The NTP also ran Ames testing on ethyl cyanoacrylate. Testing was performed using two strains. Dose levels ranged between 33 and 10,000 µg/plate, in addition to the zero dosed control. Samples were either without activation, or with activation by 10% hamster liver cells, or 10% rat liver cells[1].
These studies have not been published but it was reported in the Federal Register[2] that "ethyl cyanoacrylate was not mutagenic in the Ames test."

16) REPEATED DOSE TOXICITY
17) TOXICITY TO REPRODUCTION
18) DEVELOPMENTAL TOXICITY/TERATOGENICITY

Alkyl cyanoacrylates are among the most reactive monomers known in anionic polymerization. The mechanism of polymerization is described in the discussion on photodegradation. In the atmosphere and in biological systems, available hydroxyl ions initiate rapid polymerization of ethyl cyanoacrylate monomer. This is evidenced by the rapid bonding by instant adhesives comprising predominantly cyanoacrylate esters to skin or any other surface. This property renders ethyl cyanoacrylate a useful adhesive and makes significant exposure to ethyl cyanoacrylate monomer improbable.

As would be anticipated from this chemistry, dosing animals for repeated dose studies is problematic. Ethyl cyanoacrylate was listed by the Interagency Test Committee as a TSCA 4(e) priority chemical. After preliminary work, NTP[3] recommended its removal from the priority list citing "high reactivity of the chemical and the resulting difficulties in implementing the delivery of an effective concentration of the un-polymerized chemical to the test animals". NTP[4] also reported that they were unable to generate a stable aerosol.

The United Kingdom Health and Safety Executive has published a Risk Assessment Document on methyl and ethyl cyanoacrylate[5]. This risk assessment concluded that there are no grounds for concern for carcinogenicity at exposures below the threshold for chronic inflammatory responses in tissues at the site of contact. In addressing reproductive toxicity, they concluded "due to the reactive nature of ethyl cyanaocrylate, little systemic distribution is predicted following exposure by any physiological route. Furthermore, the overall pattern of toxicity data available suggests that the toxicological effects of ethyl cyanoacrylate would be largely restricted to local site of contact effects on the eyes and respiratory tract."

To address concerns that cyanoacrylates including ethyl cyanoacrylate may act as respiratory sensitizers capable of inducing allergic asthma, Loctite Corporation sponsored two studies. The first was a survey to determine the airborne concentrations of cyanoacrylate in a manufacturing plant[6] and the second was an

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[1] NTP unpublished results
[2] 60 FR 42987, August 17, 1995.
[3] 60 FR 42982-7, 1995
[4] NTP 1998 Annual report Table 6.
[5] Methyl cyanoacrylate and ethyl cyanoacrylate, Risk assessment document, UK Health and Safety Executive HMSO, Norwich UK, 2000.
[6] Paustenbach, D.,et al, Am. Ind. Hyg. Assoc J., 62, 70-79, 2001.

epidemiological[1] study that investigated the pulmonary effects of repeated occupational exposure to cyanoacrylates. The airborne concentrations determined in the first study provided the basis for the epidemiological study. The epidemiological study provided no evidence that those occupationally exposed to cyanoacrylate vapors during the manufacture and packaging of methyl and ethyl cyanoacrylate adhesives had any chronic pulmonary damage or that ethyl cyanoacrylate acted as a respiratory sensitizer. Subjects who had been exposed for a period of up to 18 years had no increased incidence of pulmonary obstruction compared to an unexposed population. These human exposure data render animal data of little value.

[1] Goodman M, et al, J. Toxic. & Environ. Hlth Part A , 59, 135-163, 2000.